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<b>(54) Title:</b> TREATMENT OF HEMATOLOGIC MALIGNANCIES ASSOCIATED WITH CIRCULATING TUMOR CELLS USING CHIMERIC ANTI-CD20 ANTIBODY  <b>(57) Abstract</b>  A method of treating hematologic malignancies associated with a high number of circulating tumor cells by the administration of a therapeutic chimeric anti-CD20 antibody. These malignancies include in particular B-prolymphocytic leukemia (B-PLL), chronic lymphocytic leukemia (CLL), and transformed non-Hodgkin's lymphoma.		

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**TREATMENT OF HEMATOLOGIC MALIGNANCIES ASSOCIATED  
WITH CIRCULATING TUMOR CELLS USING CHIMERIC  
ANTI-CD 20 ANTIBODY**

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**FIELD OF THE INVENTION**

The present invention is directed to the treatment of hematologic malignancies associated with high numbers of circulating tumor cells by the administration of a therapeutically effective amount of a chimeric or humanized antibody that binds to the B-cell surface antigen Bp35 (CD20).

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**BACKGROUND OF THE INVENTION**

The use of antibodies to CD20 as diagnostic and/or therapeutic agents for B-cell lymphoma has previously been reported. CD20 is a useful marker or target for B-cell lymphomas as this antigen is expressed at very high densities on the surface of malignant B-cells, i.e., those B-cells wherein unabated proliferation can lead to B-cell lymphomas.

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CD20 or Bp35 is a B-lymphocyte-restricted differentiation antigen that is expressed during early pre-B-cell development and remains until plasma cell differentiation. It is believed that the CD20 molecule may regulate a step in the B-cell activation process which is required for cell cycle initiation and differentiation. Moreover, as noted, CD20 is expressed at very high levels on neoplastic ("tumor") B-cells.

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Previous reported therapies involving anti-CD20 antibodies have involved the administration of a therapeutic anti-CD20 antibody either alone or in

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conjunction with a second radiolabeled anti-CD20 antibody, or a chemotherapeutic agent.

In fact, the Food and Drug Administration has approved the therapeutic use of one such therapeutic anti-CD20 antibody, RITUXAN®, for use in  
5 treatment of relapsed and previously treated low-grade non-Hodgkin's lymphoma (NHL). Also, the use of RITUXAN® in combination with a radiolabeled murine anti-CD20 antibody has been suggested for the treatment of B-cell lymphoma.

However, while anti-CD20 antibodies and, in particular, RITUXAN®  
10 have been reported to be effective for treatment of B-cell lymphomas, such as non-Hodgkin's lymphoma, it would be beneficial if effective antibody treatments for other malignancies could be developed. More specifically, it would be beneficial if anti-CD20 antibodies could be used for treating other types of malignancies.

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### **BRIEF DESCRIPTION OF THE INVENTION**

Toward that end, the present inventors have developed a novel treatment for hematologic malignancies characterized by a high number of tumor cells in the blood involving the administration of a therapeutically effective amount of  
20 an anti-CD20 antibody. In the preferred embodiments, such anti-CD20 antibody will comprise a chimeric, humanized or human anti-human CD20 antibody. Examples of such hematologic malignancies include B-pro-lymphocytic leukemia (B-PLL) chronic-lymphocyte leukemia (CLL) and transformed non-Hodgkin's lymphoma.

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Thus, it is an object of the invention to provide a novel treatment for hematologic malignancies comprising the administration of an anti-CD20 antibody.

It is a more specific object of the invention to provide a novel treatment  
5 for B-prolymphocytic leukemia (B-PLL), chronic lymphocytic leukemia (CLL) or transformed non-Hodgkin's lymphoma comprising the administration of an anti-CD20 antibody.

It is an even more specific object of the invention to treat B-prolymphocytic leukemia (B-PLL) or chronic lymphocytic leukemia (CLL)  
10 comprising administration of a therapeutically effective amount of RITUXAN®

### **DETAILED DESCRIPTION OF THE INVENTION**

The invention involves the discovery that hematologic malignancies and, in particular, those characterized by high numbers of tumor cells in the blood  
15 may be effectively treated by the administration of a therapeutic anti-CD20 antibody. These malignancies include, in particular, CLL, B-PLL and transformed non-Hodgkin's lymphoma.

This discovery is surprising notwithstanding the reported great success of RITUXAN® for the treatment of relapsed and previously treated low-grade non-Hodgkin's lymphoma. In particular, this discovery is surprising given the very  
20 high numbers of tumor cells observed in such patients and also given the fact that such malignant cells, e.g., CLL cells, typically do not express the CD20 antigen at the high densities which is characteristic of some B-cell lymphomas, such as relapsed and previously-treated low-grade non-Hodgkin's lymphomas.  
25 Consequently, it could not have been reasonably predicted that the CD20 antigen

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would constitute an appropriate target for therapeutic antibody therapy of such malignancies.

Treatment of hematologic malignancy, such as CLL, B-PLL and transformed non-Hodgkin's lymphoma, according to the invention will comprise the administration of a therapeutically effective amount of an anti-CD20 antibody, which administration may be effected alone or in conjunction with other treatment(s), e.g., chemotherapy, radiotherapy (e.g., whole body irradiation, or treatment with radiolabeled antibodies). In addition, combination therapy with cytokines may be useful to upregulate CD20 on the surface of the lymphoma cells.

In the preferred embodiment, the anti-CD20 antibody will bind CD20 with high affinity, i.e., ranging from  $10^{-5}$  to  $10^{-9}$ M. Preferably, the anti-CD20 antibody will comprise a chimeric, primate, primatized®, human or humanized antibody. Also, the invention embraces the use of antibody fragments, e.g., Fab's, Fv's, Fab's, F(ab)<sub>2</sub>, and aggregates thereof.

A chimeric antibody is intended to refer to an antibody with non-human variable regions and human constant regions, most typically rodent variable regions and human constant regions.

A primatized® antibody refers to an antibody with primate variable regions, e.g., CDR's, and human constant regions. Preferably, such primate variable regions are derived from an Old World monkey.

A humanized antibody refers to an antibody with substantially human framework and constant regions, and non-human complementarity-determining regions (CDRs). "Substantially" refers to the fact that humanized antibodies typically retain at least several donor framework residues (of non-human parent antibody from which CDRs are derived).

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Methods for producing chimeric, primate, primatized®, humanized and human antibodies are well known in the art. See, e.g., U.S. Patent 5,530,101, issued to Queen et al, U.S. Patent 5,225,539, issued to Winter et al, U.S. Patents 4,816,397 and 4,816,567, issued to Boss et al, and Cabilly et al, respectively, all  
5 of which are incorporated by reference in their entirety.

The selection of human constant regions may be significant to the therapeutic efficacy of the subject anti-CD20 antibody. In the preferred embodiment, the subject anti-CD20 antibody will comprise human, gamma 1, or gamma 3 constant regions and, more preferably, human gamma 1 constant  
10 regions. The use of gamma 1 anti-CD20 antibodies as therapeutics is disclosed in U.S. Patent 5,500,362, issued to Robinson et al.

Methods for making human antibodies are also known and include, by way of example, production in SCID mice, and *in vitro* immunization.

As noted, a particularly preferred chimeric anti-CD20 antibody is  
15 RITUXAN®, which is a chimeric gamma 1 anti-human CD20 antibody. The complete amino acid and corresponding nucleic acid sequence for this antibody may be found in U.S. Patent 5,736,137, which is incorporated by reference in its entirety. This antibody, which is produced in a proprietary CHO cell expression system commercialized by IDEC Pharmaceuticals Corporation, is made by a  
20 CHO cell transfectoma which was deposited on November 4, 1992, under the provisions of the Budapest Treaty at the American Type Culture Collection, located at 12301 Parklawn Drive, Rockville, MD 20852. This cell line was determined to be viable and will be replaced should it become non-viable during the term of deposit. This cell line was made irrevocably available upon issuance  
25 of the 5,736,137 patent and is available without restriction from the ATCC. This

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cell line will also be available without restriction during the lifetime of any patent that may issue based on this application.

The subject anti-CD20 antibody will be administered by various routes of administration, typically parenteral. This is intended to include intravenous, intramuscular, subcutaneous, rectal, vaginal, and administration with intravenous infusion being preferred.

The anti-CD20 antibody will be formulated for therapeutic usage by standard methods, e.g., by addition of pharmaceutically acceptable buffers, e.g., sterile saline, sterile buffered water, propylene glycol, and combinations thereof.

Effective dosages will depend on the specific antibody, condition of the patient, age, weight, or any other treatments, among other factors. Typically effective dosages will range from about 0.001 to about 30 mg/kg body weight, more preferably from about 0.01 to 25 mg/kg body weight, and most preferably from about 0.1 to about 20 mg/kg body weight.

Such administration may be effected by various protocols, e.g., weekly, bi-weekly, or monthly, dependent on the dosage administered and patient response. Also, it may be desirable to combine such administration with other treatments, e.g., radioactive therapy, both targeted and non-targeted, chemotherapies, and lymphokine or cytokine administration, e.g., interleukins, interferons, TNF's, colony stimulating factors, etc.

Typically, treatment will be effected weekly, for about 2 to 10 weeks, more typically about 4 weeks. A particularly preferred dosage regimen will comprise administration of about .375 mg/kg weekly for a total of four infusions. Also, stepped-up dosing schedules may be even more preferable.

If radiation is used in conjunction with the therapeutic anti-CD20 antibody, it is preferred that an yttrium-labeled anti-CD20 antibody we utilized,



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such as disclosed in U.S. Patent 5,736,137, incorporated by reference in its entirety herein. This antibody, 2B8-MX-DTPA, has reported efficacy in the treatment of B-cell lymphoma. The cell line that produces the 2B8 antibody has also been deposited at the American Type Culture Collection on June 22, 1993  
5 under the provisions of the Budapest Treaty, and was made irrevocably available upon issuance of US Patent 5,736,137, without any restrictions. Thus cell line was found to be viable and shall similarly be replaced during the lifetime of any patent that issues based on this application, should it become non-viable.

A particularly preferred chemotherapeutic regimen that may be used in  
10 conjunction with the subject antibody immunotherapy comprises CHOP immunotherapy, which comprises the administration of a combination of cyclophosphamide, doxorubicin, vincristine and prednisone. Other known chemotherapeutics include methotrexate, cisplatin, toremifene and tamoxifen.

The following Examples are not intended, nor are they to be construed,  
15 as limiting the invention. The Examples are intended to provide clinical evidence in support of the efficacy of the invention.

#### **EXAMPLE 1**

Two patients in whom we noted rapid reduction of blood tumor cells, which was associated with severe pulmonary infusion-related toxicity and thrombocytopenia, were studied. Also, two additional patients were collected  
20 from physician-submitted reports of adverse events related to RITUXAN® treatment. Pretreatment characterization of these patients included a median age of 60 years (range 26-73) with the diagnosis of B-prolymphocytic leukemia (B-PLL), chronic lymphocytic leukemia (CLL), or transformed non-Hodgkin's  
25 lymphoma. All of these patients had elevated leukocyte counts as a consequence of blood tumor involvement, bulky adenopathy and organomegaly. All four

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patients developed a unique syndrome of severe infusion-related reactions characterized by fever, rigors, bronchospasm with associated hypoxemia, requiring temporary cessation of RITUXAN® therapy. Concurrent with these symptoms, a rapid decrement in circulating tumor cell load (mean pretreatment 5 98 x 10<sup>3</sup>/L; range 73-132 vs. mean post-treatment 11 x 10<sup>3</sup>/L; range 37-24.6) with mild electrolyte evidence of rapid tumor lysis. Thrombocytopenia, a finding not commonly associated with RITUXAN® therapy was noted in all four patients (mean pretreatment 145 x 10<sup>3</sup>/L; range 57-277 vs. mean post-treatment 10 10<sup>9</sup>/L; range 2-120), requiring transfusion in one case. Symptoms of this syndrome required hospitalization but resolved with supportive care. Subsequent RITUXAN® treatment were well tolerated in all patients. Two subsequent patients with CLL have been treated with high blood tumor counts utilizing stepped-up dosing (100 mg day 1 followed by rest of therapy on day 1) with demonstrated efficacy, thrombocytopenia but minimal infusion-related toxicity 15 RITUXAN® administration in patients with hematologic malignancies who have blood tumor cell involvement may be associated with a higher frequency of severe initial infusion-related reactions and thrombocytopenia mandating careful clinical monitoring. Given the preliminary activity of RITUXAN® in these patients, future studies in CLL and PLL, utilizing a stepped-up dosing schedule, 20 is to be conducted.

### EXAMPLE 2

Unlabeled immunoglobulins (Mab) are attractive for the treatment of NHL as they may: mediate cytotoxicity with complement (CDC) or effector cells (ADCC); effect apoptosis; be less toxic, less immunogenic and possibly more 25 effective than toxin- or drug-conjugated Mabs; not require the complex procedures needed for radiolabeled Mab therapy (RIT), and not produce the

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myelosuppression typical of high-dose RIT. Until recently, use of Mabs in the treatment of hematologic malignancies has been limited. However, the chimeric anti-CD20 Mab, RITUXAN®, has a low toxicity profile and significant clinical efficacy and is now approved by the Food and Drug Administration (US FDA 11/97; EU 6/98) for the treatment of relapsed or refractory, low-grade or follicular (R=LG/F) NHL. In a single-agent clinical trial (PIII), of 166 patients with R-LG/F NHL treated with RITUXAN® at 375 mg/m<sup>2</sup> weekly for four infusions (study 102-05), the overall response rate (ORR) was 48% (6% CR and 42% PR). Median time to progression for responders was 13.1 months and duration of response 11.2 months. Median circulating B-lymphocyte counts dropped to zero following the first dose. CD3, CD4, CD8 and NK cell counts remained unchanged. B-cell recovery in peripheral blood began at 6-9 months and was complete by 9-12 months. No significant changes in serum complement levels were noted. The mechanism for action remains unresolved with CDC, ADCC, apoptosis and/or others being considered. In spite of the absence of a clinical/laboratory correlation, the contribution of CDC cannot be discounted. We have seen a correlation between higher absolute NK cell count at baseline and response to the Mab.

Cell Type	# Patients CR+PR	Abs. Count	# Patients NR	Abs. Count	P-value
NK	98	180	15	98	0.02
MK+ANC	98	185	15	102	0.02
ANC	101	3.7	15	3.4	0.40
CD3+	98	761	15	576	0.37
Platelets	101	187	15	206	0.32

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Note: N = 166 patients from study 102-05, and 37 from 102-06. Abs. Count: NK, CD3 = cells/mm<sup>3</sup>; ANC, Pts. = cells x 10e3/mm<sup>3</sup>. P value for the difference between Abs. Counts.

5 ADCC may be an important mechanism for the clinical activity seen in patients treated with RITUXAN®. Agents which enhance effector cell number and activity may synergize with the Mab. Studies of RITUXAN® in combination with cytokines, e.g., I1-2, G-CSF, GM-CSF, INF, are also ongoing.

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### EXAMPLE 3

#### Phase I/II Study of RITUXAN® in CLL

RITUXAN® is a monoclonal antibody targeting CD20 that has significant activity in the treatment of low-grade lymphoma (LGL). When given at a dosage of 375 mg/m<sup>3</sup> weekly/four response rate in relapsed patients (PTS) was 43% (McClaughlin et al, KOO, Vol. 14, 1998). Patients with small lymphocytic lymphoma had lower response rates (13%) than patients with other subtypes of LGL and lower serum levels of RITUXAN®. Reduced response seen in SLL could be related to lower density of CD20 antigen and/or higher circulating B-cell counts. Both factors would be expected to impact (negatively) on response seen in CLL. In an attempt to maximize activities in CLL we are conducting a Phase I/II study. All patients receive a first dose of 375 mg/m<sup>3</sup> to minimize infusion-relapsed side effects.

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Subsequent weekly dosages (3) remain the same but are given at an increased dose level. Sixteen patients have been treated at dosages of 500-1500 mg/m<sup>3</sup>. Medium age was 66 years (range, 25-78). Eighty-one percent had end-stage III-IV disease. Medium white blood cell count was 40 x 10<sup>9</sup>/L (range, 4-200), Hgb 11.6 g/dl (range, 7.7-14.7), platelets 75 x 10<sup>9</sup>/L (range, 16-160), median  $\beta_2$  immunoglobulin was 4.5 mg/L (range, 3.1-9.2). Median numbers of prior therapies was 2.5 (range 1-9). Sixty percent of patients were refractory to treatment. Two patients developed severe hypertension with the first dose (375 mgm<sup>3</sup>); another one received further therapy. Toxicity at subsequent escalated dosages has been mild although no patient at the 1500 mg/m<sup>3</sup> dose level has been fully evaluated. Eight patients have completed therapy (4 at 500 mg/m<sup>3</sup>, 3 at 650 mg/m<sup>3</sup>, 1 at 825 mg/m<sup>3</sup>). One patient treated at 560 mg/m<sup>3</sup> achieved full remission. One patient has progressive lymphocytosis on treatment and all other patients had reduction in peripheral blood lymphocytosis but less effect on lymph nodes. Dose escalation studies are ongoing.

#### EXAMPLE 4

##### Use of cytokines to upregulate the expression of CD20

Another approach to improving response in CLL patients is to upregulate the CD20 antigen using cytokines. In an *in vitro* study,

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mononuclear cells from CLL patients were incubated for 24 hours with various cytokines. Flow cytometry results showed significant up-regulation by IL-4, GM-CSF, and TNF-alpha. Venugopal P, Sivaraman S, Huang X, Chopra H, O'Brein T, Jajeh A, Preisler H. Upregulation of CD20 expression  
5 in chronic lymphocytic leukemia (CLL) cells by *in vitro* exposure to cytokines. *Blood* 1998; 10:247a. In fact, recent data suggests that the upregulation of CD20 observed on CLL cells may be limited to tumor cells (Venogopal et al. Poster - PanPacific Lymphoma meeting, June 1999. Cytokine-induced upregulation of CD20 antigen expression in chronic  
10 lymphocytic leukemia (CLL) cells may be limited to tumor cells). Preliminary data also suggest that interferon alpha also upregulates CD20 on CLL cells after only 24 hours when applied at a concentration of 500 to 1000 U/ml.

Thus, by administering certain cytokines to CLL patients prior to or  
15 concurrently with administration of Rituximab®, the expression of CD20 on the surface of malignant B-cells may be upregulated, thereby rendering CD20, as well as other cell surface markers such as CD19, a more attractive target for immunotherapy.

A collaborative study has been initiated to test for optimal cytokine  
20 doses for CD20 upregulation *in vivo*. The study protocol involves treating ten

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patients initially with GM-CSF at 250 mcg/m<sup>2</sup> SQ QD X 3, ten patients with IL-4 mcg/kg SQ QD X 3, and ten patients with G-CSF at 5 mcg/kg SQ QD X 3. Mononuclear cells will be separated by Ficon Hypaque centrifugation for apoptotic studies to determine if upregulation of CD20 translates to enhanced killing of tumor cells by Rituximab®.

#### EXAMPLE 5

##### Combination Antibody and Chemotherapy Protocol

Antibody treatment of CLL can be combined with other conventional chemotherapeutic treatments known to be useful for the treatment of CLL.

10 The most frequently used single agent for CLL is chlorambucil (leukeran), given either as 0.1 mg/kg daily or 0.4 to 1.0 mg/kg every 4 weeks. Chlorambucil is often combined with oral prednisone (30 to 100 mg/m<sup>2</sup>/d), which is useful in the management of autoimmune cytopenias.

Cyclophosphamide is an alternative to chlorambucil, the usual dose being 1-2

15 g/m<sup>2</sup> every 3-4 weeks together with vincristine and steroids (e.g., COP regimen).

Various drug combinations have been used for CLL, including COP (cyclophosphamide, Oncovin, and prednisone), and CHOP (these three drugs plus doxorubicin). Fludarabine has shown an effect in the treatment of CLL,

20 and gave an ORR of 50% in a group of patients treated with 25-30 mg/m<sup>2</sup>/d

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every 3-4 weeks. <http://www.cancernetwork.com>. Although some patients have been shown to be refractory for fludarabine. Such patients may also be resistant to 2-CdA because often, patients who are refractory to fludarabine are also refractory to 2-CDA (O'Brien et al. N. Engl. J. Med. 330: 319-322 (1994)).

Hence, anti-CD20 antibody therapy will be particularly useful for patients who are refractory or who have relapsed after treatment with chemotherapeutic drugs. Rituximab® therapy may also be combined with radiotherapy in these patients. TBI with a low fraction size of 15 cGy to total doses of 75 to 150 cGy has been shown to be effective in about one-third of patients.

A Phase II trial is currently being conducted by CALGB in CLL patients. Rituximab® and fludarabine are administered concurrently, followed by Rituximab® consolidation versus fludarabine induction followed by Rituximab®.

The goals of the study are (1) to determine in fludarabine treated CLL patients the complete response (CR) rate and toxicity profile of concurrent and consolidative Rituximab® therapy (Arm I) and of consolidative Rituximab® therapy (Arm II); (2) to assess the CR rate in patients receiving concurrent therapy with Rituximab® and fludarabine (the inductive phase of Arm I); (3)



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to assess the frequency of conversion of a partial response (PR) to a CR or stable disease to either either PR or CR in CLL patients receiving consolidative therapy with Rituximab®; (4) to follow the effects of therapy with Rituximab® and fludarabine on the immunologic markers CD4, CD8, 5 IgG, IgA and IgM; and (5) to examine progression-free survival and overall survival in Arms I and II.

Although the present invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding it will be apparent that certain changes and modifications may be practical 10 within the scope of the appended claims.

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**WHAT IS CLAIMED IS:**

1. A method of treating a hematologic malignancy associated with high numbers of circulating tumor cells by administering a therapeutically effective amount of an anti-CD20 antibody or fragment thereof.
2. The method of Claim 1, wherein said malignancy is a leukemia.
3. The method of Claim 1, wherein said malignancy is B-prolymphocytic leukemia (B-PLL) or chronic lymphocytic leukemia (CLL).
4. The method of Claim 1, wherein said antibody is a chimeric, humanized or human anti-CD20 antibody.
5. The method of Claim 1, wherein said antibody is administered at a dosage ranging from 0.1 to 30 mg/kg.
6. The method of Claim 5, wherein said dosage is administered weekly for about 2 to 10 weeks.

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7. The method of Claim 1, wherein said antibody is RITUXAN®.
8. The method of Claim 3, wherein said antibody is administered  
in combination with radiation, chemotherapy, and/or lymphokine  
5 administration.
9. The method of Claim 1, wherein said antibody is administered  
by infusion at a dosage of 375 mg/kg weekly for a total of four weeks.
10. The method of Claim 8, wherein said lymphokine is selected  
10 from the group consisting of IL-4, GM-CSF, TNF-alpha and interferon alpha.
11. The method of Claim 8 wherein said chemotherapy is selected  
from the group consisting of chlorambucil (leukeran), prednisone,  
15 cyclophosphamide, COP, CHOP and Fludarabine.
12. A method of treating a hematologic malignancy associated with  
high numbers of circulating tumor cells that is refractory to chemotherapy by  
administering a therapeutically effective amount of an anti-CD20 antibody or  
20 fragment thereof.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/26308**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(76) :A61K 39/00

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/133.1, 1.49, 143.1, 144.1, 153.1, 155.1, 173.1, 174.1, 800, 801

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN, caplus,uspatfull

anti-CD20 antigens or antibodies, hematologic malignancies, leukemia, non-Hodgkin's lymphoma, RITUXAN

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---	US 5,776,456 A (ANDERSON et al.) 07 July 1998, see claims 1-14.	1-5, 12 -----
Y		6-11
X, P ---	US 5,843,439 A (ANDERSON et al.) 01 December 1998, see entire document.	1-5, 12 -----
Y, P		6-11
X, P	Database CAPLUS, Accession No. 1999:644119, WINKLER et al. 'Cytokine-release syndrome in patients with B-cell chronic lymphocytic leukemia and high lymphocyte counts after treatment with an anti-CD20 monoclonal antibody (rituximab IDEC-C2B6)', abstract, Blood. 1999, Vol. 94, No. 7, pages 2217-2224, abstract only.	1-12

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

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Date of the actual completion of the international search 14 FEBRUARY 2000	Date of mailing of the international search report 25 FEB 2000
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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/26308

## A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

424/133.1, 1.49, 143.1, 144.1, 153.1, 155.1, 173.1, 174.1, 800, 801